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Use of EPO and/or α-MSH for preventing or treating a condition of the intestine

Field of invention

It has surprisingly been found that treatment with either α-MSH, EPO, or combined treatment with α-MSH and EPO significantly prevented hypotension, acidosis, acute renal failure and death in intestinal ischemia induced shock. Accordingly, the present invention relates to a method for treating or preventing a condition related to the tissue of the intestine of a mammal, the method comprising administration of an effective dose of an α-MSH (melanocyte stimulating hormone) and/or of an α-MSH equivalent and/or EPO (erythropoietin) and/or an EPO equivalent to an individual in need thereof. In a preferred embodiment, the invention relates to a combination of the administration to an individual in need thereof of an α-MSH and/or of an α-MSH equivalent with an EPO and/or an EPO equivalent for treatment or prevention of a condition in the tissue of the intestine. In a further aspect, the invention relates to use of α-MSH and/or of an α-MSH equivalent and/or EPO and/or an EPO equivalent for the preparation of a medicament for the treatment or prevention of a condition in the tissue if the intestine. In a still further aspect, the invention relates to a medicament comprising a combination of α-MSH and/or of an α-MSH equivalent and EPO and/or an EPO equivalent.

General background

Ischemia induced by reduced/complete arrest in arterial blood supply induce multiple tissue reactions including neutrofil accumulation, other inflammatory responses and cell death. Identification of compounds that could inhibit or prevent (either completely or partially) many of the cell/tissue/organ impairments or destructions occurring as a result of ischemia/inflammation would be of great benefit.

An example of an ischemic condition with high mortality is acute ischemia of the small intestine. The most common reasons are an embolia or an atherosclerotic thrombosis in the superior mesenteric artery. The initial symptoms are often discrete which means that the diagnose is difficult, and many patients develop severe hemodynamic disturbances with shock symptoms. The treatment is resection of the ischemic intestine or revascularisation combined with pressure support. However, the prognosis is poor with a lethality higher than 75%. Since surgical resection in most cases involves the whole ilium

with an EPO and/or an EPO equivalent for treatment or prevention of a intestine condition of the individual.

Any tissue related to the intestine may be subject to the method according to the invention. Accordingly, the condition to be treated may be located or related to any tissue selected from the group consisting ventricle, duodenum, jekunum. ileum, ceacum, appendix vermiformis, colon and rectum.

In one important aspect of the invention, the condition is due to or caused by ischemia or inflammation of the tissue such as in arterial stenosis or any other complete or partial restriction in blood supply. The ischemia may be acute or chronic depending on the severity of the disease and, furthermore, the condition may be reversible or irreversible. An example of a reversible condition may be due to fall in the blood pressure during surgery or other intervention in the blood perfusion of the organ. Accordingly, the condition may be any decrease in systemic blood flow of intestine, such as hypotension.

The method of the invention may be of special benefit in relation to conditions caused by or associated with transplantation of any organ or vessel, including prevention of graft versus host reaction. In such conditions, the entire organ is extremely sensitive to all alterations with respect to nutrition, metabolism, perfusion etc., and the treatment according to the present invention is believed to stabilize the condition and make the tissue more resistant to any situation stressing the function of the organ. The method according to the present invention also encompasses administration of an effective dose of an α-MSH and/or of an α-MSH equivalent and/or administration of an EPO and/or an EPO equivalent to the organ transplant during transport to the recipient, including addition of an effective dose of an α-MSH and/or of an α-MSH equivalent and/or administration of an EPO and/or an EPO equivalent to the transportation medium.

Other examples of conditions are diseases associated with inflammation including ulcerative colitis, Crohn's disease, other inflammatory intestinal diseases, or septicemia.

In a further aspect, the prevention and treatment may be utilized in situations caused by pericarditis, myocardiel infarction, myocardial ischemia, myocarditis, myxodemia, and endocarditis.

The condition can be associated with cardial arrhythmia. Either as the primary disease or secondary to another condition of th individual. Examples of miscellaneous causes of arrhythmia include acute infections particularly those affecting the lungs, pulmonary embolism, hypotension, shock, anoxaemia or anaemia which can precipitate myocardial ischemia and thus cause arrhythmia. The arrhythmia will aggravate the circulatory disturbance and thereby set up a vicious, self-perpetuating cycle.

Antiarrhythmic therapy performed with the aim of suppressing an arrhythmia is always associated with a risk of creating new arrhythmias. The arrhythmias may occur as a toxic reaction due to an overdose of the drug. However, particularly during treatment with the group of drugs known as Class IA drugs, arrhythmias can occur as a non dosage-dependent side effect - an idiosyncratic reaction - developing at drug concentrations well within the therapeutic range. According to a further embodiment, the condition may be causes by one or more antiarrhytmic drugs including, digitalis, quinidine, disopyramide, adenosin, aprindine, flecainide, amiodarone, sotalol, meciletine, beta blocking agents, and verapamil.

The condition related to the tissue of the intestine of the mammal can be caused by connective tissue disease such as scleroderma, systemic lupus erythematosus or by neuromyopathic disorders such as progressive muscular dystrophy of Duchenne's type, Friedreich's ataxia, and myotonic dystrophy.

The condition related to the tissue of the intestine of the mammal is caused by decrease in systemic blood flow to the intestine, heart or to other organ systems, such as hypotension.

Other conditions which may be alleviated by administration of an effective dose of an α-MSH and/or of an α-MSH equivalent and/or administration of an EPO and/or an EPO equivalent are the effect of electrolyte derangement on the organ as well as the derangement itself, including abnormalities in the relative concentrations of individual ions one to another. Such condition includes an abnormal serum concentration of one or more of the electrolytes selected from the group consisting of potassium, calcium, sodium, and magnesium

In a still further aspect, the condition may be associated with a chemical trauma involving one or more toxic substances and/or drugs. Such drugs include tricyclic antidepressants, lithium salts, prenylamine, phenothizine derivatives, chemopreventive drugs including adriamycin. Also physical traumas including electromagnetic radiation may cause damages which can be alleviated by administration of an effective dose of an α-MSH and/or of an α-MSH equivalent and/or administration of an EPO and/or an EPO equivalent according to the present invention.

The condition involved in the organ according to the present invention may further include connective tissue disease such as scleroderma, systemic lupus erythematosus or by neuromyopathic disorders such as progressive muscular dystrophy of Duchenne's type, Friedreich's ataxia, and myotonic dystrophy.

Many infections may have an influence on the tissue and disturb the normal function resulting in decreased performance which may be improved by administration of an effective dose of an α-MSH and/or of an α-MSH equivalent and/or administration of an EPO and/or an EPO equivalent. Such infections include infections by protozoa, virus, bacteria and fungus and include conditions such as AIDS, bacterial septicemia, systemic fungal infections, Rickettsial diseases, toxic shock syndrome, infectious mononucleosis, chlamydia thrachomatis, chlamydia psittaci, cytomegalovirus infection, campylobacter, salmonella, influenza, poliomyelitis, toxoplasmosis, Lassa Fever, Yellow Fever, billharziose, colibacteria, enterococcus, preteus, klebsiella, pseudomonas, staphylococcus aureus, staphylococcus epidermidis, candida albicans, tuberculosis, mumps, infectious mononucleosis, hepatitis and Coxackie virus

In a further embodiment, the intestinal condition may be caused by a cancer or a by premalignant disorder having an impact on the organ, including acute leukemia, chronic myelocytic leukemia, chronic lymphocytic leukemia, Hodgkin's disease, lymphosarcoma, myeloma, metastasizing carcinoma of any origin.

Furthermore, the condition may be caused by any disease selected from diabetes mellitus, conditions with increased fasting levels of LDL-Cholesterol, conditions with combined increased fasting levels of LDL-Cholesterol and triglycerid, conditions with increased fasting levels of triglycerid, conditions with increased fasting levels of HDL-Cholesterol, retroperitoneal fibrosis, lupus erythematosus, polyarteritis nodosa,

sclerodermia, polymyositis, dermatomyositis, rheumatoid arthritis, anaphylaxis, serum sickness, hemolytic anaemia, and allergic agranulocytosis.

In a syndrome or an arrhythmia which can be alleviated according to the present method may be either primary or secondary and may be selected from ventricular or supra ventricular tachyarrhythmias, atrioventricular block, sinus node disease, Wolff-Parkinson-White syndrome, Lenégres disease, Lev's disease any syndrome involving an abnormal myocardial connection between atrium and ventricle.

According to the present invention, the tissue of the intestine which may be affected includes one or more cell types present in the organ and may be selected from macrophages, the reticulo endothelial system monocytes, neutrophil granulocytes, eosinophil granulocytes, basophil granulocytes, T-cells, B-cells, mast cells, and dendritic cells. Especially, the T-cells, B-cells, and mast cells may be of certain interest in this respect.

In a further aspect of the invention, the condition may be characterised by one or more abnormalities as measured by electrocardiography (ECG). The abnormality on the ECG may relate to an alteration selected from one or more changes in the configuration selected from the P wave, the ST segment, the T wave, the QRS complex, the Q wave, the delta wave, and the U wave.

A preferred aspect of the invention relates to prevention or treatment wherein a dose of an α-MSH and/or of an α-MSH equivalent and/ or an EPO and/or an EPO equivalent or a combination thereof is administered profylactically for preventing a progress of the condition or of any symptom of the condition.

Accordingly, the dose of α-MSH and/or of an α-MSH equivalent or an EPO and/or an EPO equivalent or a combination thereof is administered profylactically for prevention of the establishment of the condition or of any symptom of the condition.

The dose of α-MSH and/or of an α-MSH equivalent or an EPO and/or an EPO equivalent or the combination thereof may be administered as a single dosage, regular or continued administration, or as a sequential administration.

The administration may be parenteral administration, such as intraperitoneal administration, intrathecal administration, systemic administration, local administration including use of drug target systems and implants, topical administration, transmucosal administration, transdermal administration and/or oral administration.

Accordingly, the administration includes systemic administration; injection into tissue or into a body cavity including joints; implantation into tissue or into a body cavity; topical application to the skin or to any gastrointestinal surface, or to a mucosal surface including the lining of body cavities.

The α-MSH equivalent according to the present invention is preferably a substance acting on an α-MSH receptor and/or on the melanocortin receptor such as subtypes 1 to 5 (MC-receptors 1-5) and/or a substance which has immunosuppressive activity as determined in the test described in US 5,830,994. Such substances are disclosed in e.g. EP 972522, WO 87/04623, WO 88/00833, WO 99/57148, WO 99/21571, WO 96/41815, US 5,028,592, US 5,731,408, US 5,830,994 and the references cited therein.

In a further important aspect, the α-MSH equivalent is a polypeptide having at least 3 amino acids including the following sequence Lys-Pro-Val, such as Gly-Lys-Pro-Val, or the following sequence His-Phe-Arg, and being able to act on an α-MSH receptor.

The EPO equivalent according to the present invention is preferably a substance acting on an EPO receptor. Such substances are disclosed in e.g. US 5,835,382, US 5,986,047, WO00/32772 and PNAS 96, no. 21 (1999), 12157 and the references cited therein. An important EPO equivalent is a peptide having the sequence QRVEILEGRTECVLSNLRGRTRY.

In an embodiment of the invention, a hybrid peptide of an EPO equivalent and an α-MSH equivalent can be used, e.g. a peptide having the sequence QRVEILEGRTECVLSNLRGRTRY-X-SYSMEHFRWGKPV, where X is a molecular linker having the formula:

1) GGGS,
2) A-(G-G-G-G-S)3-T,
3) A-(G-G-G-G-S)2-T,
4) A-(G-G-G-G-S)-T,

5) No linker (a peptide bond) or

6) A amino acid sequence (e.g. having 1-6 α-amino acids)

In a preferred embodiment, the α-MSH, α-MSH equivalent, EPO, EPO equivalent or the hybrid thereof is in the form of a recombinantly produced protein.

A very important aspect of the present invention is the beneficial effect of the combination of the use of an α-MSH or an α-MSH equivalent with an EPO and/or an EPO equivalent as the combination has an additive effect on the condition to be treated. An additive effect may be measured as an effect increasing any of the effects of the individual drugs used in the same dosage. Additionally, it is believed that the combination in most circumstances will have a synergistic effect. A synergistic effect may be measured as an effect increasing the sum of the individual effect of each of the individual drugs used in the same dosage. A synergistic effect may also include the situation where an effect equal to the sum of effects by the individual treatments is obtained with minor doses of the individual drugs than when used in combination.

In a still further aspect, the present invention relates to the use of an α-MSH and/or an α-MSH equivalent or of an EPO and/or an EPO equivalent or a combination of an α-MSH and/or of an α-MSH equivalent with an EPO and/or an EPO equivalent for the preparation of a medicament for treatment or prevention of any of the conditions disclosed herein.

The preparation of a medicament according to the present invention includes medicaments for injection or systemic administration, such as a medicament in a form suitable for injection or systemic administration, e.g. a solution or a suspension.

The medicament may be for implantation including implants or other devices wherein the medicament is incorporated into a coating of a medico technical device or is incorporated into the material of the device itself, including artificial heart valves and stents. The active ingredients may be incorporated into or onto the device by use of a suitable polymer.

Furthermore, the medicament may be prepared for topical application in the form of a powder, paste, ointment, lotion, gel, cream, emulsion, solution, suspension, spray, aerosol, sponge, strip, plaster, or pad. Furthermore, the medicament may be prepared for oral administration in the form of tablets, sustained release tablets, or resoritablets. When

for topical application, the m dicament may be prepared in the form of a preparation suitable for application on mucosa e.g. a suppository, a tampon, a suspension for irrigation, a tablet or troche, a cream or gel or ointment; or for application on urethral mucosa, a bladder insert, or an implant.

The α-MSH and/or α-MSH equivalent or EPO and/or EPO equivalent or the combination thereof may be present in the medicament in an amount of 0.001-99%, typically 0.01-75%, more typically 0.1-20%, especially 1-15 such as 1-10% by weight of the medicament.

The dose depends on the conditions to be treated. The individual drugs may be used in the doses known in the art. However, according to the present invention minor doses will generally be sufficient. With respect to the use of the combination, the EPO may very often be effective in rather small doses. The necessary dose of EPO in the combination may be such a dose which, when used alone, would not have any significant effect on the condition.

In a still further aspect, the present invention relates to a pharmaceutical composition comprising a combination of α-MSH or and/or α-MSH equivalent and EPO and/or an EPO equivalent with a pharmaceutically acceptable carrier. In an interesting aspect, the α-MSH or α-MSH equivalent and EPO and/or an EPO equivalent is a physical entity.

The pharmaceutical compositions according to the present invention may be prepared by use of conventional techniques known in the art and with conventional pharmaceutical carriers. Furthermore, the pharmaceutical composition may be in any form suitable for any of the uses as described herein.

Preferably, the pharmaceutical composition is in a form as described above.

Legends to figures

Figure 1. Mean Arterial pressure before, during and after 45 minutes occlusion of the coliac trunk and the superior mesenteric artery in vehicle treated rats, rats treated with rh-

EPO (200 U/kg b.w.), rats treated with α-MSH (200 µg/kg b.w.) or rats treated with the combination of rh-EPO (200 U/kg b.w.) and α-MSH (200 µg/kg b.w.).

Figure 2. Glomerular filtration rate before, during and after 45 minutes occlusion of the coliac trunk and the superior mesenteric artery in vehicle treated rats, rats treated with rh-EPO (200 U/kg b.w.), rats treated with α-MSH (200 µg/kg b.w.) or rats treated with the combination of rh-EPO (200 U/kg b.w.) and α-MSH (200 µg/kg b.w.).

Figure 3. Arterial blood pH before, during and after 45 minutes occlusion of the coliac trunk and the superior mesenteric artery in vehicle treated rats, rats treated with rh-EPO (200 U/kg b.w.), rats treated with α-MSH (200 µg/kg b.w.) or rats treated with the combination of rh-EPO (200 U/kg b.w.) and α-MSH (200 µg/kg b.w.).

Figure 4. Arterial blood HCO_3^- before, during and after 45 minutes occlusion of the coliac trunk and the superior mesenteric artery in vehicle treated rats, rats treated with rh-EPO (200 U/kg b.w.), rats treated with α-MSH (200 µg/kg b.w.) or rats treated with the combination of rh-EPO (200 U/kg b.w.) and α-MSH (200 µg/kg b.w.).

Examples

Barrier-bred and specific pathogen-free female Wistar rats (210-230 g) were obtained from the Department of Experimental Medicine, Panum Institute, University of Copenhagen, Denmark. The animals were housed in a temperature (22-24°C) and moisture (40-70%) controlled room with a 12-hour light-dark cycle (light on from 6:00 A.M. to 6:00 P.M.). All animals were given free access to tap water and a pelleted rat diet containing approximately 140 mmol/kg of sodium, 275 mmol/kg potassium and 23 % protein (Altromin catalogue no. 1310, Altromin International, Lage, Germany).

Animal preparation.

Rats were anesthetized with halothane-nitrous oxide and permanent medical grade Tygon catheters were implanted into the abdominal aorta and into the inferior caval vein via a femoral artery and vein. Catheters were produced, fixed and sealed as described by Petersen et al. (J. Pharmacol. Exp. Ther. 258: 1-7, 1991). After instrumentation, the animals were housed individually. All surgical procedures were performed during aseptic

conditions. To relieve postoperative pain, rats were treated with buprenorfin, 0.2 mg/kg b.w. i.p. (Anorfin, GEA A/S, Copenhagen, Denmark). Two to three days later the rats were anesthetized with halothane-nitrous oxide and instrumented with a peruretral bladder catheter. The rats received constant i.v infusion of 150 mM Glucose with ^{3}H-Inulin throughout, infusion rate 3.5 ml/hr. Then the coeliac trunk and the superior mesenteric artery were isolated near the aortic origins through a midline laparotomy. A 60 minutes calibration period was followed by a 30 minutes control period. Then the coeliac trunk and the superior mesenteric artery were clamped for 45 minutes followed by four hours reperfusion. MAP and HR was followed throughout. Urine was collected in a 30 minutes control period, during the 45 minutes ischemia period and in four one-hour periods during reperfusion. Arterial blood samples for measurement of ^{3}H-Inulin were collected at the end of each urine collection period. Arterial blood samples for measurements of pH and HCO_3^- were collected at the end of the control period, at the end of the ischemic period and at the end of the experiment. The body temperature was kept constant at 37° C throughout the experiment.

Experimental groups:

All the rats were subjected to ischemia/reperfusion. After 30 minutes ischemia the rats were subjected to one of the following i.v. treatments (N=6 in all groups):

Vehicle: 0.5 ml 150 ml Glucose

rh-EPO: 200 I.U. epoitin alfa (EPO)/kg b.w. in 0.5 ml Glucose.

α-MSH: 200 µg α-melanocyte stimulating hormone (α-MSH)/kg b.w. in 0.5 ml 150 ml Glucose.

α-MSH+rh-EPO: 200 µg α-MSH and 200 I.U.EPO/kg b.w. in 0.5 ml 150 ml Glucose.

Analytical procedures:

Urine volume was determined gravimetrically. Concentrations of sodium and lithium in plasma and urine were determined by atomic absorption spectrophotometry using a Perkin-Elmer (Allerød, Denmark) model 2380 atomic absorption spectrophotometer.^{3}H-Inulin in plasma and urine were determined by dual label liquid scintillation counting on a Packard Tri-Carp liquid scintillation analyser, model 2250CA (Packard Instruments, Greve, Denmark). Arterial blood pH and HCO_3^- were measured by use of an ABL 555 (Radiometer, Copenhagen, Denmark).

Statistics

Data are presented as mean ± S.E.. Within groups comparisons were analysed with Students paired *t* test. Between groups comparisons were performed by one way analysis of variance followed by Fishers L ast Significant Difference test. Differences were considered significant at the 0.05 level.

Survival

Table 1 summarizes survival rate and time in the four experimental groups. The vehicle treated rats all died within three hours after reperfusion. One of the animals treated with rh-EPO died 185 minutes after reperfusion and one of the α-MSH treated animals died 155 minutes after reperfusion. The rest survived the four hours reperfusion period. All rats that received combined treatment with rh-EPO and α-MSH survived throughout.

Mean Arterial Pressure (Figure 1)

Occlusion of the splanchnic arteries produced a significant increase in MAP in all rats. Reperfusion of the splanchnic arteries produced severe hypotension in the vehicle treated rats. This hypotensive response to reperfusion was significantly blunted in rats treated with rh-EPO or α-MSH. However, neither rh-EPO nor α-MSH could stabilize MAP at a level above the lower limit of renal perfusion pressure autoregulation (renal function, see later). Combined treatment with rh-EPO and α-MSH had a much more pronounced effect on MAP. The initial fall in MAP after reperfusion was almost completely abolished, and at the end of the 4 hours reperfusion period MAP was still above the lower limit of renal perfusion pressure autoregulation (84 ± 4 mmHG).

Renal Function (Figure 2)

Reperfusion of the splanchnic arteries significantly reduced glomerular filtration rate (GFR) in all groups. The reduction was most pronounced in the vehicle treated group with a complete stop in urine production two hours after reperfusion. Treatment with rh-EPO or α-MSH was unable to protect against further decreases in GFR during reperfusion, with the result that GFR was reduced by 71% in the rh-EPO and by 91% in α-MSH treated rats, respectively.

Combined treatment with rh-EPO and α-MSH significantly blunted the initial fall in GFR, and compared to treatment with either rh-EPO or α-MSH the combined treatment prevented any further decrease in GFR. In fact, the initial fall in GFR was partly reversed

during the next four hours, and at the end of the experiment GFR was only reduced by 32% compared to the pre-SAO level.

Acidosis (Figures 3 and 4)

Occlusion/reperfusion of the splanchnic arteries produced severe acidosis in all rats. Treatment with rh-EPO, α-MSH or the combination of the two reduced the acidosis. However only the combination treatment was able to reverse the acidosis.

Claims

1. A method of treating or preventing a condition in the tissue of the intestine or other organs of a mammal comprising administration of an effective dose of an α-MSH and/or of an α-MSH equivalent, or an EPO and/or an EPO equivalent, or a combination of an α-MSH and/or of an α-MSH equivalent with an EPO and/or an EPO equivalent to an individual in need thereof.

2. A method according to claim 1, wherein the tissue is selected from group consisting of ventricle, duodenum, jejunum, ileum, ceacum, appendix vermiformis, colon and rectum.

3. A method according to any of the preceding claims, wherein the condition is caused by ischemia or inflammation of the tissue.

4. A method according to claim 3, wherein the ischemia or inflammation of the tissue is acute or chronic.

5. A method according to any of the preceding claims, wherein the condition is reversible or irreversible.

6. A method according to any of the preceding claims, wherein the condition is caused by artery stenosis or other complete or partial restriction in blood supply.

7. A method according to any of claims 1-6, wherein the condition is caused by or associated with surgery of any kind or transplantation of any organ or vessel, including prevention of graft versus host reaction.

8. A method according to any of claims 1-5, wherein the condition is selected from diseases associated with inflammation including ulcerative colitis, Crohn's disease, other inflammatory intestinal diseases, or septicemia.

9. A method according to any of the preceding claims, wherein the condition is caused by pericarditis, myocardiel infarction, myocardial ischemia, myocarditis, myxodemia, endocarditis.

10. The method according to any of the claims 1-5, wherein the condition is associated with cardial arrhythmia.

11. The method according to any of claims 1-5, wherein the condition is causes by one or more antiarrhytmic drugs including, digitalis, quinidine, disopyramide, adenosine, aprindine, flecainide, amiodarone, sotalol, meciletine, beta blocking agents, and verapamil.

12. The method according to any of the claims 1-5, wherein the condition is caused by connective tissue disease such as scleroderma, systemic lupus erythematosus or by neuromyopathic disorders such as progressive muscular dystrophy of Duchenne's type, Friedreich's ataxia, and myotonic dystrophy.

13. A method according to any of claims 1-5, wherein the condition is caused by decrease in systemic blood flow to the intestine, heart or to other organ systems, such as hypotension.

14. A method according to any of claims 1-5, wherein the condition is caused by electrolyte derangement including abnormalities in the relative concentrations of individual ions one to another.

15. A method according to claim 14, wherein the condition is caused by an abnormal serum concentration of one or more of the electrolytes selected from the group consisting of potassium, calcium, sodium, and magnesium.

16. A method according to any of claims 1-5, wherein the condition is caused by or associated with a chemical trauma including a toxic substance and/or drug such as a drug selected from the group consisting of tricyclic antidepressants, lithium salts, prenylamine, phenothizine derivatives and chemopreventive drugs including adriamycin.

17. A method according to any of claims 1-5, wherein the condition type is caused by electromagnetic radiation.

18. A method according to any of claims 1-5, wherein the condition is caused by an infection by protozoa, virus, bacteria and/or fungus, such as AIDS, bacterial septicemia,

systemic fungal infection, Rickettsial disease, toxic shock syndrome, infectious mononucleosis, chlamydia thrachomatis, chlamydia psittaci, cytomegalovirus infection, campylobacter, salmonella, influenza, poliomyelitis, toxoplasmosis, Lassa Fever, Yellow Fever, billharziose, colibacteria, enterococcus, proteus, klebsiella, pseudomonas, staphylococcus aureus, staphylococcus epidermidis, candida albicans, tuberculosis, mumps, infectious mononucleosis, hepatitis and Coxackie virus

19. A method according to any of claims 1-5, wherein the condition is caused by a cancer or a by premalignant disorder having an impact of the heart, including acute leukemia, chronic myelocytic leukemia, chronic lymphocytic leukemia, Hodgkin's disease, lymphosarcoma, myeloma, metastasizing carcinoma of any origin.

20. A method according to any of claims 1-5, wherein the condition is caused by any disease selected from diabetes mellitus, conditions with increased fasting levels of LDL-Cholesterol, conditions with combined increased fasting levels of LDL-Cholesterol and tryglycerid, conditions with increased fasting levels of triglycerid, conditions with increased fasting levels of HDL-Cholesterol, retroperitoneal fibrosis, lupus erythematosus, polyarteritis nodosa, sclerodermia, polymyositis, dermatomyositis, rheumatoid arthritis, anaphylaxis, serum sickness, hemolytic anaemia, and allergic agranulocytosis.

21. A method according to any of the preceding claims, wherein the condition is selected from ventricular or supra ventricular tachyarrhythmias, atrioventricular block, sinus node disease, Wolff-Parkinson-White syndrome, Lenégres disease, Lev's disease any syndrome involving an abnormal myocardial, connection between atrium and ventricle.

22. The method according to any of the preceding claims, wherein the condition is characterised by one or more abnormalities as measured by electrocardiography (ECG).

23. The method according to any of the preceding claims, wherein the condition as measured by ECG relates to an alteration selected from in one or more changes in the configuration selected from the P wave, the ST segment, the T wave, the QRS complex, the Q wave, the delta wave, and the U wave.

24. A method according to any of the preceding claims, wherein the dose of a combination of an α-MSH and/or of an α-MSH equivalent with an EPO and/or an EPO

quivalent is administered profylactically for preventing a progress of the condition or of any symptom of the condition.

25. A method according to any of the preceding claims, wherein the dose of a combination of
α-MSH and/or of an α-MSH equivalent with EPO and/or an EPO equivalent is administered profylactically for preventing the establishment of the condition or of any symptom of the condition.

26. A method according to any of the preceding claims, wherein the dose of an α-MSH and/or of an α-MSH equivalent or an EPO and/or an EPO equivalent or a combination thereof is administered as a single dosage, regular or continued administration, or as a sequential administration.

27. A method according to any of the preceding claims, wherein the tissue comprises one or more cell types selected from macrophages, the reticulo endothelial system monocytes, neutrophil granulocytes, eosinophil granulocytes, basophil granulocytes, T-cells, B-cells, mast cells, and dendritic cells.

28. A method according to claim 27, wherein the cell type is selected from T-cells, B-cells, and mast cells.

29. A method according to any of the preceding claims, wherein the administration is selected from parenteral adminstration, including intraperitoneal administration, intrathecal administration, systemic administration, local administration, topical administration, transmucosal administration, transdermal administration, and oral administration.

30. A method according to any of the preceding claims wherein the administration is selected from systemic administration; injection into tissue or into a to body cavity including joints; implantation into tissue or into a body cavity; topical application to the skin or to any gastrointestinal surface, or to a mucosal surface including the lining of body cavities.

31. A method according to any of the preceding claims wherein the α-MSH equivalent is a substance acting on the α-MSH receptor and/or on the melanocortin receptor such as subtypes 1 to 5 (MC-receptors 1-5).

32. A method according to any of the preceding claims, wherein the α-MSH equivalent is a polypeptide having at least 3 amino acids including the following sequence Lys-Pro-Val, such as Gly-Lys-Pro-Val, or the following sequence His-Phe-Arg,

33. A method according to claim 32, wherein the combination of α-MSH and/or α-MSH equivalent with EPO and/or EPO equivalent has an additive effect.

34. A method according to claim 32 wherein the combination of α-MSH and/or α-MSH equivalent with EPO and/or EPO equivalent has a synergistic effect.

35. Use of an α-MSH and/or of an α-MSH equivalent, an EPO and/or an EPO equivalent, or a combination of an α-MSH and/or of an α-MSH equivalent with an EPO and/or an EPO equivalent for the preparation of a medicament for treatment or prevention of a condition in the tissue of the intestine.

36. Use according to claim 35 for the preparation of a medicament for injection or systemic administration, such as a medicament in a form suitable for injection or systemic administration, e.g. a solution or a suspension.

37. Use according to claim 35 for the preparation of a medicament for implantation, characterised in that the medicament is incorporated into a coating of a medico technical device or is incorporated into the material of the device itself.

38. Use according to claim 35 for the preparation of a medicament for topical application in the form of a powder, paste, ointment, lotion, gel, cream, emulsion, solution, suspension, spray, aerosol, sponge, strip, plaster, or pad.

39. Use according to claim 35 for the preparation of a medicament for oral administration in the form of tablets, sustained release tablets, or resoritablets.

40. Use according to claim 35 for the preparation of a medicament for topical application in the form of a preparation suitable for application on mucosa e.g. a suppository, a tampon, a suspension for irrigation, a tablet or troche, a cream or gel or ointment; or for application on urethral mucosa, a bladder insert, or an implant.

41. Use according to any of claims 35-40 wherein the α-MSH and/or α-MSH equivalent or EPO and/or an EPO equivalent or the combination thereof is present in the medicament in an amount of 0.001-99%, typically 0.01-75%, more typically 0.1-20%, especially 1-10% by weight of the medicament.

42. A pharmaceutical composition comprising a combination of α-MSH and/or α-MSH equivalent and EPO and/or EPO equivalent together with a pharmaceutically acceptable carrier.

43. The pharmaceutical composition according to claim 42 wherein the α-MSH and/or α-MSH equivalent and EPO and/or an EPO equivalent is a physical entity.

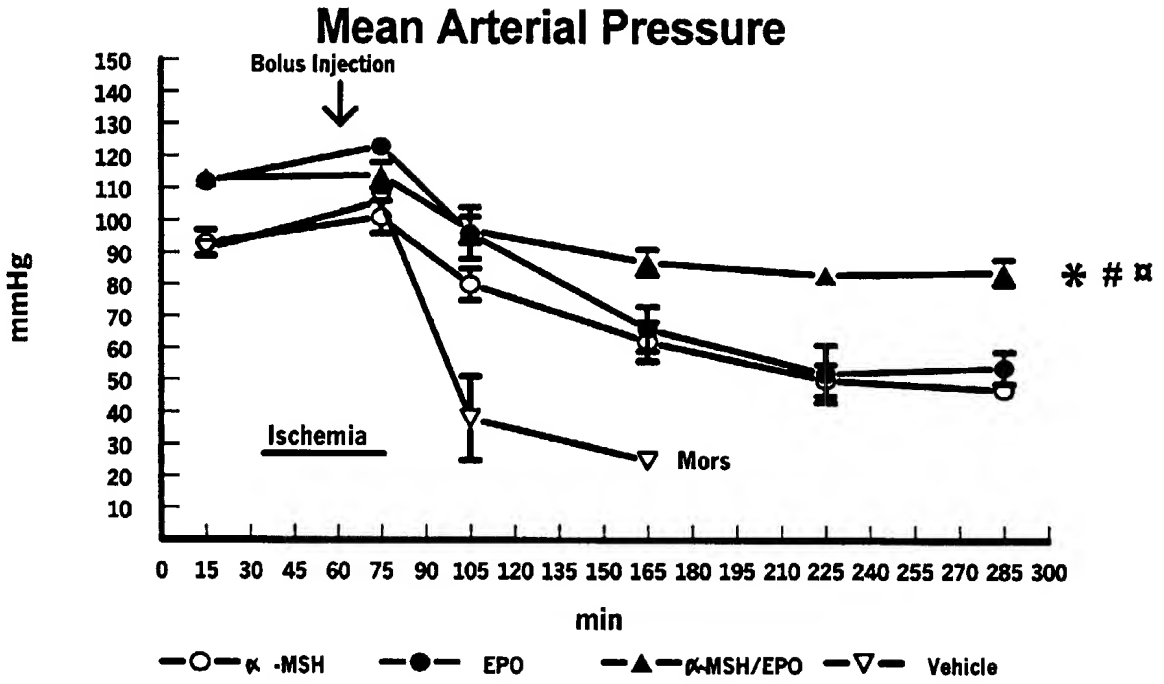
44. The pharmaceutical composition according to any of claims 42 and 43 in a form as described in any of the claims 36-40.

45. A peptide having the sequence QRVEILEGRTECVLSNLRGRTRY.

46. A peptide having the sequence QRVEILEGRTECVLSNLRGRTRY-X-SYSMEHFRWGKPV, where X is a molecular linker having the formula:

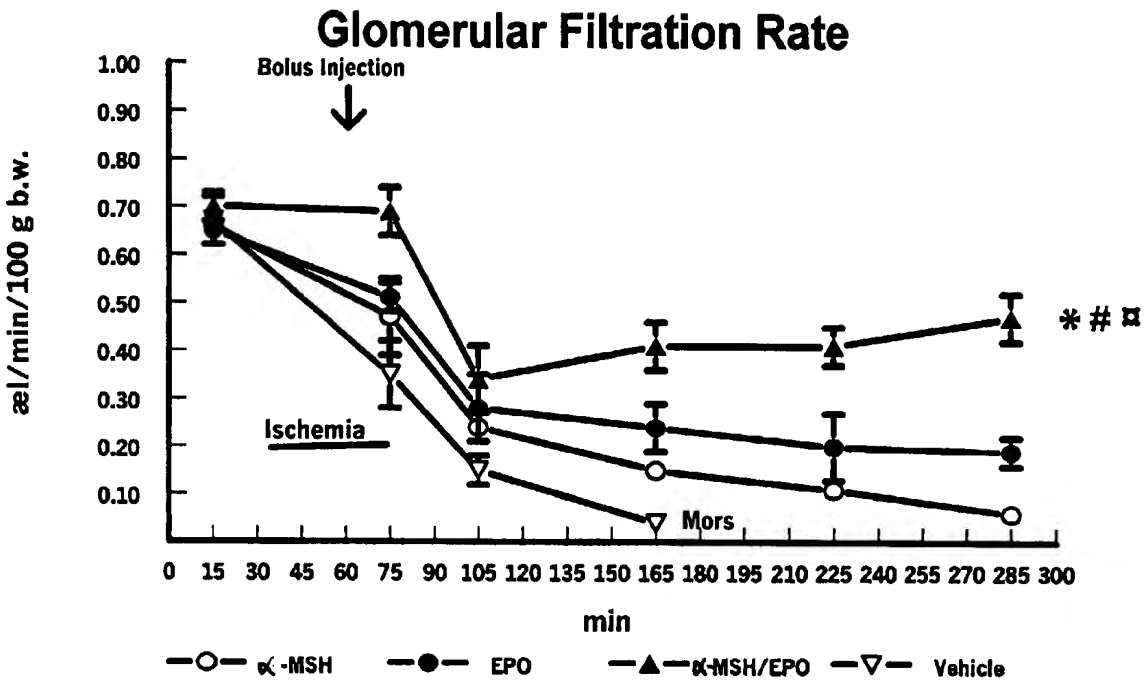
1) GGGS,
2) A-(G-G-G-G-S)3-T,
3) A-(G-G-G-G-S)2-T,
4) A-(G-G-G-G-S)-T,
5) No linker (a peptide bond) or
6) A amino acid sequence (e.g. having 1-6 α-amino acids)

Figure 1



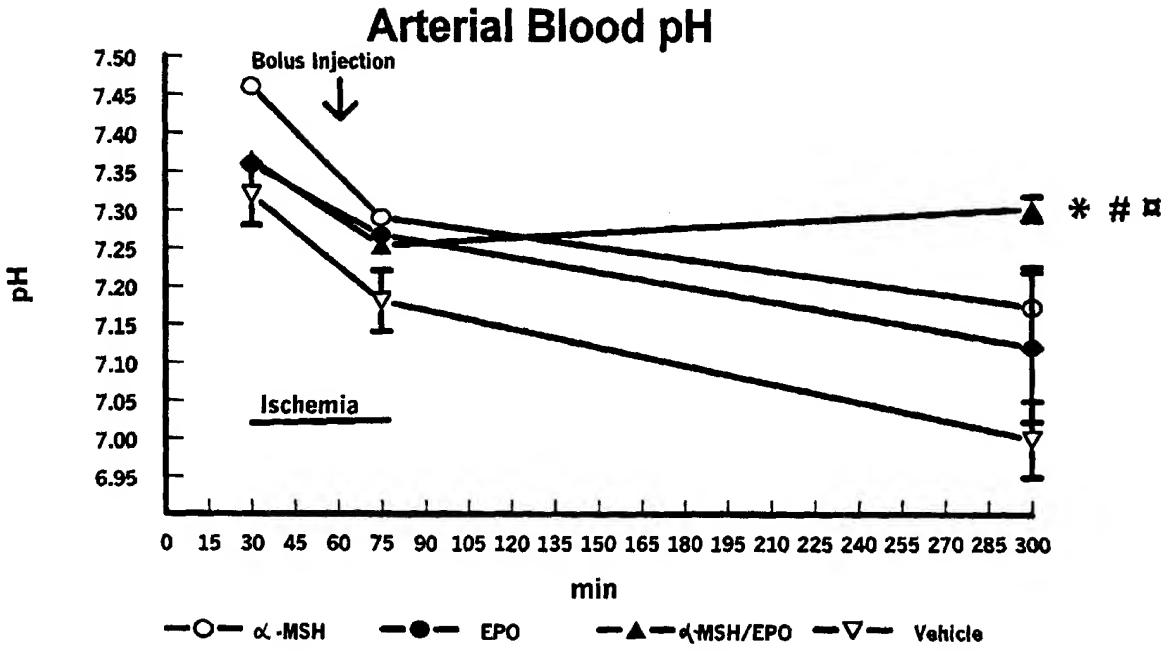
Mean Arterial pressure before, during and after 45 minuts occlusion of the coliac trunk and the superior mesenteric artery in vehicle treated rats, rats treated with rh-EPO (200 U/kg b.w.), rats treated with α-MSH (200 µg/kg b.w.) or rats treated with the combination of rh-EPO (200 U/kg b.w.) and α-MSH (200 µg/kg b.w.). *: different from Vehicle treated rats; $p<0.05$; #: different from rh-EPO treated rats; $p<0.05$; ¤: different from α-MSH treated rats; $p<0.05$.

Figure 2



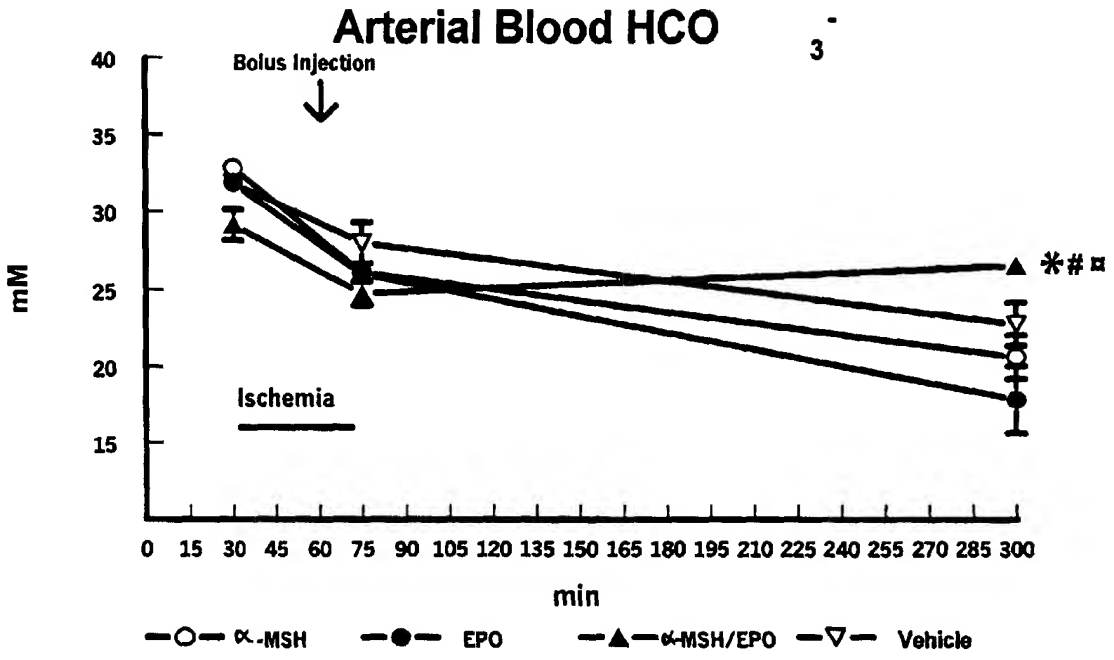
Glomerular filtration rate before, during and after 45 minuts occlusion of the coliac trunk and the superior mesenteric artery in vehicle treated rats, rats treated with rh-EPO (200 U/kg b.w.), rats treated with α-MSH (200 µg/kg b.w.) or rats treated with the combination of rh-EPO (200 U/kg b.w.) and α-MSH (200 µg/kg b.w.). *: different from Vehicle treated rats; $p<0.05$; #: different from rh-EPO treated rats; $p<0.05$; ¤: different from α-MSH treated rats; $p<0.05$.

Figure 3



Arterial blood pH before, during and after 45 minuts occlusion of the coliac trunk and the superior mesenteric artery in vehicle treated rats, rats treated with rh-EPO (200 U/kg b.w.), rats treated with α-MSH (200 µg/kg b.w.) or rats treated with the combination of rh-EPO (200 U/kg b.w.) and α-MSH (200 µg/kg b.w.). *: different from Vehicle treated rats; $p<0.05$; #: different from rh-EPO treated rats; $p<0.05$; ¤: different from α-MSH treated rats; $p<0.05$.

Figure 4



Arterial blood HCO_3^- before, during and after 45 minuts occlusion of the coliac trunk and the superior mesenteric artery in vehicle treated rats, rats treated with rh-EPO (200 U/kg b.w.), rats treated with α-MSH (200 µg/kg b.w.) or rats treated with the combination of rh-EPO (200 U/kg b.w.) and α-MSH (200 µg/kg b.w.). *: different from Vehicle treated rats; $p<0.05$; #: different from rh-EPO treated rats; $p<0.05$; ¤: different from α-MSH treated rats; $p<0.05$.

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